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Role of *Chlamydia pneumoniae* as an Inducer of Asthma

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1. INTRODUCTION

1.1. Definition of Induction

Chlamydia pneumoniae (Cpn) could have three distinguishable causal effects as an asthma inducer. First, an acute infection (or reactivation of a latent infection) could cause an acute worsening of preexisting asthma. Indeed, it is generally accepted that acute Cpn infection can cause some acute asthma *exacerbations*[1,2] but most evidence suggests that other organisms [mainly respiratory viruses, and, to a lesser extent, *Mycoplasma pneumoniae* (Mpn[3])] are associated with the majority of asthma exacerbations in both children[4] and adults.[5] Second, because of its propensity to produce persistent infection, Cpn chronic lung infection could cause worsening of established asthma over time. Again, Cpn has been associated with asthma severity[6] and a possible *promoting* role for Cpn in asthma is a focus of active investigation.[7] Third, an acute primary or secondary Cpn infection, in a previously asymptomatic nonasthmatic individual, could cause acute wheezing that develops into chronic asthma. That Cpn can *initiate* asthma is a radical idea for which there is some evidence[8] but how important a role Cpn plays as an asthma initiator remains to be determined. It is conceivable that acute Cpn infection, as an asthma initiator, could contribute to a substantial number of cases. This chapter focuses on the substantial body of evidence favoring a promoting role for Cpn, and also reviews the existing evidence for Cpn as an asthma initiator.

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1.2. Definition of Asthma

Asthma can be defined either by diagnostic or functional criteria. This distinction is important. In the United States, clinicians try to make clear-cut diagnostic distinctions between asthma, chronic bronchitis, and emphysema whereas in European countries, particularly the Netherlands, the tendency is to view these diseases as a continuum. This debate between "splitters"[9] and "lumpers"[10] has not been resolved to everyone's satisfaction. American asthma specialists have tended to view asthma as a noninfectious allergic (atopic) condition beginning in childhood and also have tended to diagnose older patients with asthma symptoms as chronic obstructive pulmonary disease (COPD), particularly if a history of smoking was present.[11] It is now apparent from population-based epidemiological studies that (1) neither atopy[12] nor allergen exposure[13] are primary causes for childhood asthma, (2) half of asthma may be related to nonatopic (neutrophilic) rather than to atopic (eosinophilic) inflammation,[14,15] and (3) adult-onset asthma (AOA) is as frequent as childhood-onset asthma.[16] Of further interest are data showing that smoking is associated with Cpn infection as well as COPD.[17,18]

The natural history of obstructive airways syndromes may evolve over a lifetime,[19,20] airway-disease-related variables (age, sex, smoking, pulmonary function, and markers for atopy) have unimodal and continuous distributions across clinical diagnoses,[21] and a significant minority of patients with asthma-like symptoms cannot be placed in the classical diagnostic categories.[10,21] To avoid diagnostic bias, it is probably more scientifically accurate to view atopy and smoking, along with other factors associated with asthma (e.g. bronchial hyper responsiveness), as covariates rather than as diagnostic attributes. For purposes of population-based, patient-outcome-oriented primary care clinical research, I favor the use of a functional definition for asthma based solely on cardinal symptoms (cough, wheeze, chest tightness, shortness of breath) and objective evidence for reversible airways obstruction determined by lung function testing.

Persistent symptomatic reversible airway obstruction is a common entity encountered in primary care settings.[16,21] The majority of cases are diagnosed as asthma, but the "overlap" syndromes [chronic asthmatic bronchitis and asthma with chronic airways obstruction (AS-CAO[22])] are often difficult to distinguish from asthma in clinical practice, respond to similar treatments, are linked to asthma in epidemiological studies and may represent later stages in the natural history of reversible airway obstruction.[10,19,22] The concept that asthma and COPD might have a common underlying etiopathology characterized by a unique host response to exogenous stimuli was proposed by Orie[23] and has become known as the "Dutch Hypothesis." The Dutch refer to obstructive airways syndromes (asthma and COPD) as *chronic nonspecific lung disease* (CNSLD),[10] and chronic Cpn infection has been proposed as an etiologic factor in CNSLD.[20] As well as reviewing the evidence for a role in the initiation and promotion of asthma, this chapter also reviews the evidence suggesting a role for Cpn in the development of lung remodeling, a cardinal feature of COPD.

1.3. Importance of Asthma

Asthma is an important cause of respiratory morbidity (symptoms, impaired quality of life, medication side effects), health care utilization (clinic and emergency room visits, hospitalizations, medication costs), and mortality. National costs for asthma in the USA were over $6 billion in 1990[24] and are steadily increasing since asthma prevalence leaped almost 20%, from 10.4 million to 12.4 million, between 1990 and 1992[25,26] and continues to rise. The history of an "infectious initiation"[27] and markers for chlamydial infection[28] may be significant risk factors for the development of COPD from nonatopic AOA. If COPD sequelae are included in the equation, costs of asthma are much greater than currently reported, since more than 16 million adults have COPD, and COPD accounts for approximately 110,000 deaths per year, $18 billion in direct health care costs and almost $10 billion in indirect costs.[29,30]

The incidence of asthma is greatest in childhood but the prevalence of active asthma is equally distributed between children and adults because of the longer period of time available for accrual of new cases of adult asthma[31] and the greater likelihood for asthma remission to occur in childhood-onset compared to AOA.[32] These facts account for the data that, nationally, patients 18 years or older account for 72% of direct costs, 61% of indirect costs, and 66% of overall costs of asthma care, excluding medications.[24] In one clinical setting, adults 19 years or older accounted for 51% of the costs of asthma treatment, including medications.[33] Death from asthma is a rare event in children, but asthma mortality increases steadily with age such that the mortality rate in the elderly population (age 70 and older) can be more than 40 times the death rate in children aged 14 or less.[34] It has been hypothesized that this age-related asthma mortality is due to the premature development of fixed obstruction known to accompany long-standing asthma.[35] These utilization data correlate with the clinical picture of asthma derived from numerous observations: compared with childhood-onset asthma, adult-onset asthma is associated with fewer markers of atopy,[36] more likely to affect women,[37] more clinically severe,[38,39] less likely to remit,[40,41] and associated with more fixed obstruction.[22,42,43]

1.4. Current Asthma Treatments Are Palliative, Not Curative

Current asthma treatment is based on a paradigm of asthma as a noninfectious atopic condition whose "root cause" is inflammation.[44,45] It is now well established that chronically administered antiinflammatory medications, primarily inhaled corticosteroids (ICS), ameliorate asthma symptoms and improve prebronchodilator FEV_1 (forced expiratory volume in 1 s).[46–49] However, the therapeutic effects of ICS treatment are not maintained upon discontinuation,[47] implying that ICS treatment is for the most part suppressive (palliative), not curative. The hoped-for additional effect that ICS treatment prevents the accelerated development of fixed obstruction in childhood asthma is not supported by evidence.[50,51] A randomized controlled trial found that ICS administration failed to slow the decline of postbronchodilator FEV_1 in adult

asthma,[49,52] and an uncontrolled, before–after observational trial in adults found that postbronchodilator FEV_1 actually declined more rapidly after the addition of ICS.[35] Any new asthma therapy that is superior to antiinflammatory drugs could have significant impacts on asthma morbidity, mortality, and costs of care.

2. *Chlamydia pneumoniae* AS A PROMOTER OF ASTHMA SEVERITY

Cpn-specific total Ig and the isotypes IgG and IgA antibodies have been associated with asthma in many studies of adults,[53] but serologic studies in childhood asthma have been mixed.[54,55] Conversely, several studies using culture or polymerase chain reaction (PCR) testing have shown high prevalence of Cpn in the upper airways of children with asthma,[54,56,57] but Cpn is rarely detected in upper-airway samples of adult asthmatics, although Cpn has been detected in adult asthmatic lower airways.[58,59] Furthermore, many studies have found that Cpn antibodies were associated with adult asthma severity.[6,7,54,57,60–64] It is generally recognized that children do not develop antibodies against Cpn as readily as adults and therefore serology is a less reliable marker of possible chronic infection in children as compared with adults. Conversely, positive serology in adults could indicate previous exposure rather than persistent infection so that serologic associations in the absence of organism detection in the lung are not conclusive evidence for infection. Thus, currently available serologic evidence upon which most of the Cpn–asthma associations are based serves as a basis for more detailed investigation but is not in itself proof of causation. This further evidence must include results of antichlamydial antibiotic treatment studies in asthma that are confounded by potential antiinflammatory effects of the agents employed and by uncertainty about whether persistent Cpn infection can be eradicated by currently available antibiotic treatments. Thus, it will be challenging to produce conclusive evidence that chronic Cpn infection causes or contributes to persistent asthma.

2.1. *Chlamydia pneumoniae*–Asthma Serologic Associations

A 1999 review of 18 controlled epidemiological studies containing over 4000 cases and controls reported significant associations between Cpn and asthma in 15 of 18 studies.[53] An additional 12 positive case–control studies were presented at the 2000 Meeting of the European Society for Chlamydia Research and at the 2000 European Respiratory Society Meeting.[63,65–75] Some of these studies found significant associations with PCR positivity in airway secretions as well as with Cpn-specific antibodies. Overall, the 27 positive studies included both children and adults with asthma; some reported stronger associations with nonatopic asthma than with atopic asthma, but differentiation on the basis of atopy was not universal. Some studies that measured only IgG antibodies failed to detect significant differences between cases and controls,[76–78] whereas studies that included IgA antibodies were more often positive.[7,53,79–82] A number of

recently published seroepidemiologic studies add further evidence for a significant association between asthma and Cpn-specific IgA[7,79–81] and also with chlamydial heat shock protein–60 (Hsp60) antibodies.[63,66,83] The latter observation, of an association between asthma and chlamydial Hsp60 antibodies, is intriguing because of the established link between chlamydial Hsp60 seroreactivity and the known chlamydia-caused diseases—trachoma, pelvic inflammatory disease, and tubal infertility.[84–86]

Several studies have found evidence that acute Cpn infection, when present in acute exacerbations of asthma[82,87] or of chronic bronchitis[88] is associated with increased sputum neutrophil and eosinophil cationic protein levels,[82] asthma exacerbation severity,[87] and chronic bronchitis exacerbation frequency.[88] A larger number of studies have found significant associations between markers of possible chronic infection and markers of asthma severity (Table I).

Cpn-specific antibodies, in the absence of acute infection, have been associated with asthma severity as measured by asthma symptom frequency,[61] number of exacerbations,[56] quantity of inhaled corticosteroid medication use,[62] and symptom severity classification.[7] Especially Cpn-specific IgA antibodies, both in serum[6,7,62,63] and in sputum[63] or nasal washings,[56] have been associated with asthma severity, suggesting that this short-half-life antibody may be a useful marker for chronic infection.[79] Two preliminary treatment studies, one in children[54] and one in adults,[61] also suggest that macrolide treatment for Cpn-associated asthma is more successful in less severe disease and before the occurrence of lung remodeling.

2.2. Results of Antibiotic Treatment Directed against Chlamydial Infection in Asthma

2.2.1. Macrolide Antibiotics Have Been Used in Asthma, but Indications and Mechanisms Are Unclear

A role for triacetyloleandomycin (TAO), a macrolide antibiotic, in the treatment of asthma was first suggested in 1959.[90] It remains unclear to what extent antiasthma effects of TAO and other macrolides may be related to "steroid sparing" activity,[91–93] inhibition of theophylline clearance,[94] direct antiinflammatory effects,[95–97] or to other mechanisms such as direct antiviral activity.[98] Early[99] and more recent[100] clinical observations indicated that TAO and erythromycin might improve symptoms and bronchial hyperresponsiveness, respectively, in patients who were not receiving corticosteroids or theophylline. These observations suggest that effects on steroid and theophylline metabolism alone cannot account for the antiasthma properties of macrolides. Of additional interest is a preliminary report of prolonged remissions in severe asthma after withdrawal of long-term TAO therapy.[101] Because remission of severe asthma is unusual, this observation begs an explanation, as antiinflammatory or antiviral effects of macrolides are expected to wane soon after treatment discontinuation. An antibiotic effect was first suggested by clinical observations documenting

TABLE I
Studies Finding Associations Between *Chlamydia pneunoniae* Infection and Asthma Severity

Reference	Asthma population/ Study design	Results
Emre *et al.*[54]	12 Cpn culture-positive children/Case series	Macrolide treatment was less effective in more severe asthma.
Hahn *et al.*[60]	Grp1: 12 adults with persistent asthma; Grp2: 30 adults with intermittent asthma; Grp3: 89 with nonwheezing respiratory illnesses/Case–control	Cpn seropositivity (total Cpn-specific Ig titers > 1:16) was strongly associated with asthma severity (100% of Grp1, 80% of Grp2, 53% of Grp3, $P < 0.001$). Antibody geometric mean titer (GMT) was also associated with severity (Grp1 = 76, Grp2 = 29, Grp3 = 19, $P = 0.0001$).
Hahn[61]	46 Cpn seropositive adults (some culture positive)/ Before–after trial	Macrolide treatment was less effective in asthma patients with a coexisting component of fixed obstruction.
Cook *et al.*[6]	1518 nonasthmatic hospital controls, 123 acute asthma patients with exacerbations admitted to hospital (chronic bronchitis and COPD excluded), 46 severe chronic asthma outpatients/Case–control	Chronic/recent infection (IgG64-256 or IgA ≥ 8) present in 12.7% of controls, 14.6% of exacerbations, and 34.8% of severe asthma (Odds ratio 3.99, 95% confidence interval 3.6–9.9, for severe asthma versus controls).
Cunningham *et al.*[56]	108 children with asthma, aged 9–11, enrolled in a 13-month longitudinal community-based study/ Prospective cohort	Cumulative frequency of Cpn PCR+ in nasal washings was 45% (independent of symptom status). Children with multiple exacerbations were more likely to remain PCR+ ($P < 0.02$). Amount of Cpn-specific secretory IgA was more than 7 times higher in children with four or more exacerbations versus 1 exacerbation ($P < 0.02$).
Black *et al.*[62]	619 adult asthma patients/Nested case–control	Use of high-dose inhaled corticosteroids (ICS) was associated with increased Cpn-specific IgG ($P = 0.04$), and IgA ($P = 0.0001$) seropositivity compared to use of low-dose ICS. In patients with IgG ≥ 1:64 and/or IgA ≥ 1:16, there was an inverse association between IgG and FEV_1 ($P = 0.04$) and IgA antibodies were associated with a higher daytime asthma symptom score ($P = 0.04$).

TABLE I
(Cont.)

Reference	Asthma population/ Study design	Results
Huittinen *et al.*[63]	105 mild–moderate asthmatics and 33 healthy controls/ Case–control	Serum IgA heat shock protein–60 (Hsp60) antibodies (40% cases, 22% controls, $P < 0.05$), sputum IgA (51% cases vs. 25% controls, $P < 0.01$) and sputum IgA Hsp60 (41% vs. 22%, $P < 0.05$) correlated with asthma severity.
Schmidt *et al.*[89]	106 children (66 male, 40 female, ages 1 month to 17 years) undergoing bronchoscopy for therapy-resistant obstructive symptoms and/or recurrent or chronic bronchitis/ pneumonia, without identification of any other cause/Nested case–control	52% were PCR+ on BAL (half were strongly positive and half were weakly positive; the investigators suggest that weak positives might indicate chronic infection). Compared to PCR– children, PCR+ children had less eosinophilia of the nasal mucosa, less total serum IgE antibodies, and worse pulmonary function. However, weak positive PCR patients had the highest rates of allergic sensitization, reduction in lung volume, and the most obstruction.
Von Hertzen *et al.*[7]	116 adults with asthma from a chest clinic (31 men, 85 women; 13 severe, 54 moderate, 49 mild asthma) and 50 blood donor controls (31 men, 19 women)/ Case–control	Severe and moderate asthma were significantly associated with elevated IgA antibody titers to Cpn: ORs were 5.6 (95% CI 1.3–24) for severe asthma and 5.7 (2–16) for moderate asthma. cHsp60 antibodies were more frequent and of higher titer among asthmatics than controls but the differences were not significant.

prolonged asthma improvement and even remission after microbiologic eradication of Cpn in infected asthma patients.[54,58,61] The first randomized, controlled trial of a macrolide to treat asthma[102] documented a significant treatment effect on morning peak expiratory flow rate (PEFR) immediately after treatment but this result could have been due either to an antiinflammatory or to an antibiotic effect.[103] It is now recognized that macrolides possess significant antiinflammatory effects that may be useful to treat a variety of chronic inflammatory lung diseases.[104] The dramatic beneficial effect of low-dose, long-term macrolide treatment in diffuse panbronchiolitis (DPB), a chronic inflammatory lung disease prevalent in Japan,[105] is an example. Cpn had been continuously isolated from a patient with DBP,[106] but chlamydial infection does not appear to contribute significantly to the etiology,[107] establishing macrolides as having a profound nonantibiotic effect in DPB that requires continuous therapy to maintain benefit. Another example is cystic fibrosis, in which significant macrolide treatment benefit has been demonstrated and interpreted as due to

an antiinflammatory effect;[108] however, some cases of CF have been associated with Cpn infection.[109] Current controversy surrounds the issue whether beneficial effects of macrolide treatment for asthma and related conditions are due to antiinflammatory[110] or to antibiotic[111] mechanisms, but all parties agree that future randomized, controlled trials are warranted to resolve this issue.[103,111] Distinguishing an antiinflammatory mechanism from an antibiotic one is important, among other reasons, because of implications for length of treatment.

2.2.2. *Antichlamydial Antibiotic Treatment for Asthma*

Table II summarizes results of preliminary treatment studies that support the need for further randomized trials. Table III illustrates that the positive treatment effect of antibiotics may be equivalent to or greater than that of inhaled corticosteroids (ICS).

2.2.2a. Randomized Controlled Trials

Evidence for a promoting role for chronic Cpn infection in asthma requires randomized treatment trials for confirmation.[115] No randomized, controlled trials (RCTs) in children and two RCTs of antichlamydial treatment for adult asthma have been published[102,116] (Table I). Kraft *et al.*[114] reported that 31 of 55 (56%) adults with asthma were PCR positive for *M. pneumoniae* (Mpn), Cpn, or both in bronchoalveolar lavage (BAL) fluid or bronchial biopsy and that only PCR-positive subjects randomized to 6 weeks of clarithromycin treatment had improved pulmonary function and reduced expression of IL-5, suggesting an antibiotic rather than an antiinflammatory effect. Black *et al.*[102] randomized 232 adults with asthma and serologic evidence of previous Cpn exposure to 6 weeks of roxithromycin therapy and reported that this macrolide treatment was associated with a significant improvement in morning peak expiratory flow rate (PEFR) at the end of treatment. Although the level of improvement in morning PEFR in treated subjects was maintained, the significant difference from the control group was no longer present at 3 and 6 months because of steady gradual improvement in the control group. Therefore, the results of this study leave unanswered the question whether Cpn is important in asthma.[103] The Black *et al.*[102] trial contained methodological deficiencies, including lack of (1) monitoring for changes in asthma controller medications (to control for "medication confounding": the potential for changing doses of controller medication in the usual care setting), (2) performance of direct organism detection (indicating whether subjects were actually infected at baseline, whether treatment eradicated infection, and whether cessation of treatment was followed by reestablishment of infection), and (3) inclusion of a control group of asthmatic patients with asthma of similar severity but without evidence of infection (to determine whether observed effects were a result of antiinflammatory activity).[103] My group recently completed a multisite randomized, placebo-controlled pilot feasibility trial employing 6 weekly doses of azithromycin in 45 adult primary care outpatients with persistent asthma and found consistent 3-month posttreatment trends favoring azithromycin for all measures of asthma-specific symptoms, rescue medication use, and quality of life

TABLE II
Treatment Results Supporting a Causal Role for Cpn Infection in Asthma

Reference	Asthma population/ Study design	Results
Emre *et al.*[54]	12 Cpn culture-positive children/Case series	Lasting improvement in symptoms and pulmonary function associated with microbiologic eradication of Cpn.
Hahn[61]	46 Cpn seropositive adults (some culture positive)/ Before–after trial	25 had lasting improvement or complete remission in symptoms and improved pulmonary function.
Hahn *et al.*[112]	1 adolescent & 2 adults with severe, steroid-dependent asthma and serologic evidence suggesting Cpn infection/Case series	Significant improvement after prolonged antibiotics; all three able to discontinue oral steroids.
Hahn *et al.*[58]	Case of nonatopic AOA/Case report	Improvement in asthma symptoms, FEV_1 and quality-of-life documented after microbial eradication of Cpn from BAL[a] fluid.
Espositio *et al.*[113]	71 wheezing children of whom 24 had Mpn or Cpn infection/ Nonrandomized treatment	Macrolide treatment significantly decreased relapse rate in Mpn/Cpn infected children (0 vs. 69% relapsed within 3 months) although 2/3 Cpn PCR+ cases remained PCR+ after treatment.
Black *et al.*[102]	232 Cpn seropositive adults/RCT[b]	Roxithromycin group (6-week treatment) had persisting increase in PEF[c] that was statistically significant only at 6 weeks.
Kraft *et al.*[114]	55 adult asthmatics of whom 31 were PCR positive for Mpn or Cpn/RCT[b]	Only PCR+ asthmatics receiving clarithromycin (6-week treatment) had significantly improved pulmonary function and decreased IL-5 cytokine expression in BAL.
Hahn *et al.* (unpublished)	45 adult asthmatics/pilot RCT[b]	Consistent trends in favor of azithromycin (6-week treatment) for all measures of asthma symptoms, rescue medication use and asthma-specific quality of life 3 months posttreatment.

[a]Bronchoalveolar lavage.
[b]Randomized, controlled trial.
[c]Peak expiratory flow.

(Hahn, D. L., Plane, M. B., personal communication). Positive effects 3 months after treatment cessation are consistent with an antibiotic mechanism. Our preliminary results need to be confirmed by larger trials before firm conclusions can be drawn, however.

In summary, elevated antibody titers to Cpn, but not to other organisms, are associated with asthma.[64] Many studies find that Cpn titers are associated with markers for asthma severity and that the association is stronger for long-standing

TABLE III
Comparison of Open-Label Results of Azithromycin vs. Blinded Result of Inhaled Corticosteroids on FEV_1 in Asthma

		Control Groups			Treated Groups		
	Study duration, months.	No. of subjects	Baseline FEV_1[a]	% change	No. of subjects	Baseline FEV_1[a]	% change
RCTs: inhaled corticosteroids							
Haahtela *et al.*[48]	24	53	87%	0	50	87%	+4
Juniper *et al.*[46]	12	16	90%	0	16	92%	0
Kerstjens *et al.*[49]	30	183	63%	−1	91	65%	+10[†]
Vathenen *et al.*[47]	1 1/2	16	98%	−6	18	96%	+8
Azithromycin							
Hahn[61]	6	–	–	–	46	68%	+12

[a]Percent predicted [†]maximum response at 3 months postreatment, then FEV_1 declined 0.033L/year (same as in control group).

than for recent-onset asthma.[117] These data have been interpreted to indicate that Cpn is primarily a promoter rather than an initiator of asthma.[64] It has also been acknowledged, however, that the data do not exclude a role for Cpn in asthma initiation.[7]

3. *Chlamydia pneumoniae* AS AN ASTHMA INITIATOR

3.1. Asthma Is Often Associated with Preceding Respiratory Illnesses

Patients developing AOA often recall that their asthma symptoms started after an acute respiratory illness such as acute bronchitis, pneumonia, or an influenza-like illness.[27] Clinical observations[118,119] and prospective epidemiological studies[120–122] also support an association between bronchitis/pneumonia and subsequent AOA. While these observations have often been interpreted to suggest that the preceding illnesses were actually misdiagnosed asthma symptoms or merely viral exacerbations of previously unrecognized asthma, a third possibility is that acute infectious illnesses might actually play a role in asthma initiation. Epidemiological associations of respiratory illness and subsequent asthma also pertain to children[123] and adolescents.[124] The risk of developing asthma has been associated with close household contact with nonrelatives (friends and spouses).[125] This observation could be explained by an infectious agent as a cause for asthma.[126]

3.2. New-Onset Asthma after Acute Cpn Infection

Soon after the discovery of the TWAR organism (now called *C. pneumoniae*) several case reports of asthma initiation after acute Cpn infection were published.[127–129] Subsequently, I and my colleague, Roberta McDonald, performed a prospective study that included 10 adult outpatients presenting

in primary care clinical practice with a first-ever reported wheezing attack, representing all such cases encountered over a 10-year time period.[8] All 10 patients met serologic criteria for an acute primary ($n = 8$) or an acute secondary ($n = 2$) Cpn infection using criteria that included a fourfold or greater titer rise and/or presence of Cpn-specific IgM antibody. Six of the 10 had persistent wheezing symptoms that eventually met American Thoracic Society criteria for chronic asthma ($n = 5$) or chronic bronchitis ($n = 1$). The latter patient was Cpn-culture-positive during the chronic bronchitic phase of his illness.[8] After 6 months to 2 years of persisting symptoms, all subjects were treated with prolonged courses of antibiotics with antichlamydial activity, and asthma symptoms resolved completely in every case.[61] Further details on these patients are presented in Table IV. These data linking serologic evidence of acute Cpn infection with new-onset asthma that appeared to respond to antimicrobial treatment strongly suggest the possibility that Cpn can initiate asthma in previously asymptomatic individuals. Attempts to replicate these findings are of high priority to determine the quantitative contribution of Cpn infection to new-onset asthma. In my opinion, this research must include prospective studies in primary care settings where most acute lower respiratory illnesses and new-onset asthma present.

3.3. Infection Should Be Added to the List of Possible Causes for Worldwide Increases in Asthma

A consensus exists that asthma prevalence and mortality have been increasing worldwide in recent decades, but the reasons for these changes in frequency and severity of disease are unknown.[130] None of the proposed risk factors (e.g., changes in atopy, smoking, air pollution, poor housing, better-insulated housing, etc.) appear to explain these temporal trends.[131] Strachan[131] has pointed out that quite large changes in the level of relatively powerful causal agents are required to explain documented increases in asthma prevalence. An infectious disease pandemic represents one candidate as a powerful causal agent. A role for Cpn infection as a cause for worldwide increases in asthma is plausible and has been suggested.[132] Ecologic data show that Cpn infection[133] and asthma[134] in all age groups and in both sexes have increased simultaneously in Finland over recent decades. Considering the possibility that worldwide increases in asthma are due to an infectious disease pandemic, further research into the Cpn–asthma association assumes great importance.

4. SUMMARY: *Chlamydia pneumoniae* AS AN ASTHMA INDUCER

A growing body of evidence (based on culture isolation, polymerase chain reaction (PCR) detection, serologic studies, and treatment results) links Cpn infection with asthma primarily in adults,[53,59,135] and in children as well.[54,56] Nonatopic asthma has been associated with an infectious initiation in general[27] and with Cpn infection in particular.[8,117,128] Cpn respiratory tract infections can initiate asthma[8] and are present in up to one-half of adults with asthma.[116] It is even possible that the contribution of Cpn infection to asthma is so great

TABLE IV
Clinical Data[a] in 10 Patients with *Chlamydia pneumoniae* Infection and *de novo* Wheezing[b]

Age, Sex	Date	Total Ig	IgM	IgG	IgA	Clinical description
1. 37, M	10/13/88 (4 days)[c]	128	16			Bronchitis with wheezing
	11/14/88	128	0			
	9/13/89	128	0			No asthma
2. 39, M	11/21/88 (5 days)	0	16			Laryngitis, bronchitis with wheezing
	12/23/88	256	128			
	4/17/89	64	16			
	6/29/89	32	0			No asthma
3. 59, F	3/9/89 (7 days)	16	32			Pneumonia with wheezing
	4/3/89	256	512			
	7/28/89	64	64			
	11/27/89	32	0			No asthma
4. 35, F	8/22/89 (24 days)	512	0			Bronchitis with wheezing[d]
	10/16/89	4096	0			
	9/18/91	256	0			No asthma
5. 55, M	1/26/89 (4 days)	64	16			COPD, pneumonia with wheezing
	1/10/92	512	0	256	256	Asthma diagnosed
	2/6/92	256	0	256	256	
6. 47, F	3/21/89 (48 days)	256	16			Bronchitis with wheezing
	4/21/89	256	0			Persistent wheezing
	9/16/89	256	0			Asthma diagnosed
	2/3/92	256	0	256	16	
	3/5/92	512	0	256	16	
	2/18/93	256	0	512	16	
	5/26/93	256	0	256	16	
	1/17/96	256	0		32	
7. 51, M	4/24/90 (35 days)	256	64			COPD, bronchitis with wheezing
	5/21/90	128	128			Persistent wheezing
	11/11/91	256	0	128	16	Asthma diagnosed
	12/11/91	256	0	128	16	
	3/6/92	256	0	128	16	
	2/19/93	256	0	128	16	
8. 39, F	10/29/93 (3 days)	32	0		<8	Bronchitis with wheezing
	3/24/94	128	0		16	Asthma diagnosed
9. 56, M	4/11/94 (70 days)	512	256		≥64	Community-acquired pneumonia with wheezing
	6/17/94	1024	32		≥64	Chronic bronchitis diagnosed[d]
	3/31/95	512	8		64	
10. 35, F	7/7/94 (66 days)	1024	128		≥64	Bronchitis with wheezing
	8/5/94	1024	64		≥64	Persistent wheezing
	10/17/94	1024	16		≥64	
	12/19/94	1024	8		≥64	Asthma diagnosed

[a]Reprinted with permission of *Ann. Allergy Asthma Immunol.* 1998;339–344. Copyright 1998.
[b]Defined as the first-ever wheezing episode experienced by the patient. Missing IgG and IgA results were due to unavailability of sera.
[c]Days post illness onset.
[d]Culture positive.

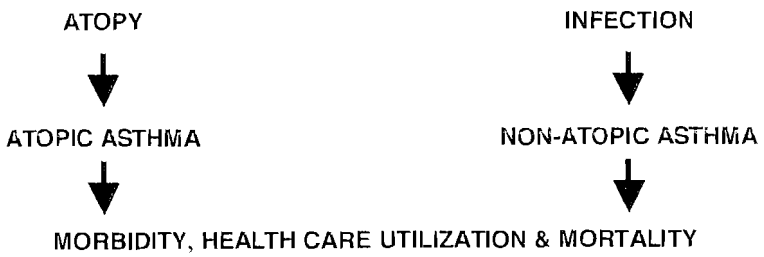

FIGURE 1. Schematic illustration of current model of dual etiologies—atopy and infection—producing atopic and nonatopic asthma syndromes, respectively.

that infection has played a role in causing worldwide increases in reactive airway diseases over the past several decades. The emerging concept of infection as a potential contributing cause for asthma is illustrated in Fig. 1.

5. *Chlamydia pneumoniae* AND LUNG REMODELING

5.1. Infection May Also Be Related to Airway Remodeling in Asthma and COPD

The combination of adult-onset nonatopic asthma and Cpn seroreactivity has been associated specifically with an accelerated decline in lung function, suggesting that Cpn infection could contribute to the development of lung remodeling and COPD (Fig. 2). Ten Brinke *et al.* studied 101 adults with severe asthma recruited from outpatient pulmonary clinics at 10 Dutch hospitals.[28] Fifty-one percent (52 subjects) had early-onset asthma (before age 18) and 49% had AOA, with 24 subjects (24%) having adult-onset nonatopic asthma associated with IgG antibody positivity against Cpn. This latter group exhibited a decline in lung function that was 4 times greater than the other three groups combined (2.3% per year for Cpn-positive nonatopic AOA versus 0.5% per year for other subjects). Early-onset and adult-onset study groups were well matched in age, sex, asthma severity, pulmonary function, serologic parameters, and smoking status. The rate of decline of lung function in this cross-sectional, retrospective study was comparable to that reported in prospective studies, and recall bias could not explain the differences predicted by serological status.[28] The authors suggest that "The striking association between seropositivity to *C. pneumoniae* and increased decline in lung function in AOA is compatible with the hypothesis that this respiratory pathogen might be involved in airway remodeling."[28]

Additional studies[53] have described associations between Cpn serology and COPD, and it has been hypothesized that Cpn infection augments smoking-associated inflammation in COPD.[136] Cpn has been documented by PCR, immunohistochemistry (IHC), and/or electron microscopy (EM) in COPD,[137,138] and also in emphysema,[139] lung tissue. These observations are compatible with the idea that chronic chlamydial lung infection may relate to the pathogenesis of established chlamydial diseases such as trachoma, pelvic inflammatory disease and tubal infertility that involve inflammation, and fibrosis and scarring

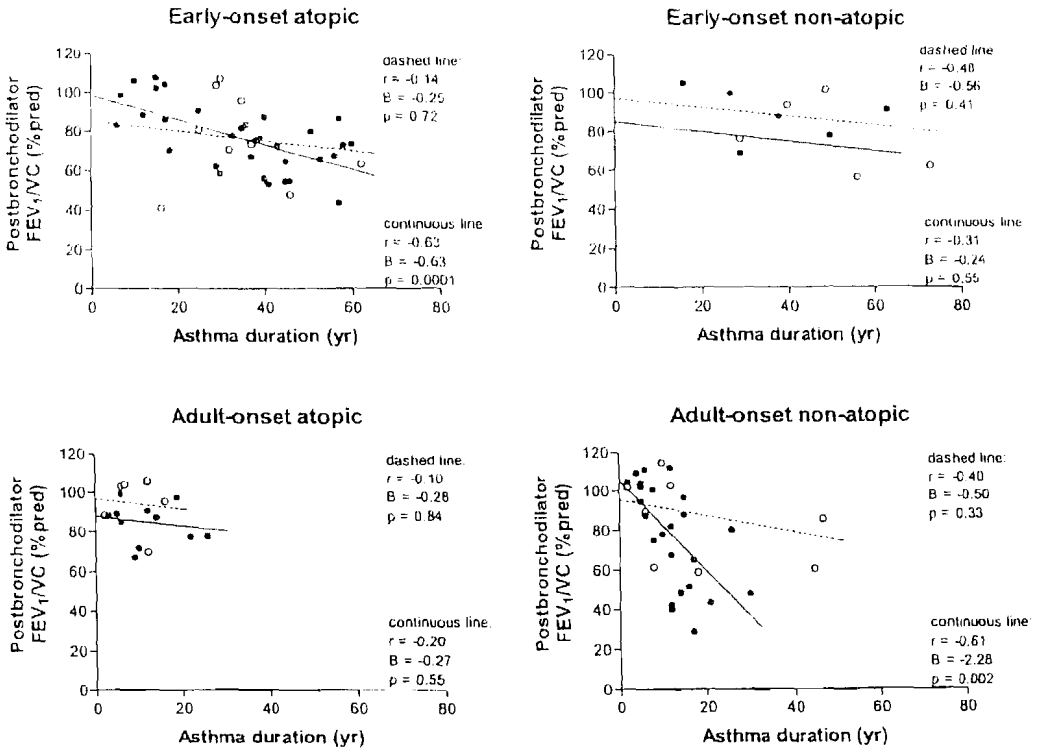

FIGURE 2. Relationship between asthma duration and postbronchodilator FEV_1/VC (percent predicted [% pred]) in different subgroups of patients with severe asthma according to age of onset of asthma, atopic status, and *C pneumoniae* IgG seropositivity (filled circles and continuous lines) versus seronegativity (open circles and dashed lines). Only in the subgroup of patients with adult-onset nonatopic asthma was a significant difference ($P = 0.03$) in the slopes of the regression lines observed. B, Slope of the regression line, with corresponding P value. Reprinted from *J. All. Clin. Immunol.* **107**, ten Brinke *et al.*, "Persistent airflow limitation in adult-onset nonatopic asthma is associated with serologic evidence of *Chlamydia pneumoniae* infection," pp. 449–54, Copyright (2001), with permission from Elsevier Science.

resulting from an immunopathologic host response to chronic infection. A recent randomized trial of long-term, low-dose erythromycin in COPD reported profound beneficial effects of the macrolide on incidence of mild and severe COPD exacerbations but provided no information about the underlying mechanism of action.[140] These epidemiological and histologic studies are complemented by a variety of *in vitro* and *in vivo* pathogenesis studies that are reviewed below.

5.2. Cpn Produces Cytokines Linked to Asthma and Lung Remodeling

In vitro studies have demonstrated that Cpn infection of relevant lung cells can produce cytokines associated with asthma inflammation.[141] Potential pathogenic factors include release of reactive oxygen species, TNF-alpha, IL-1beta, and IL-8 from *in vivo* and *ex vivo* Cpn infected alveolar macrophages[142] and IL-8, prostaglandin-E2, ICAM-1, cyclooxygenase-2 and NF-kB upregulation in human airway epithelial cells, in association with transepithelial migration

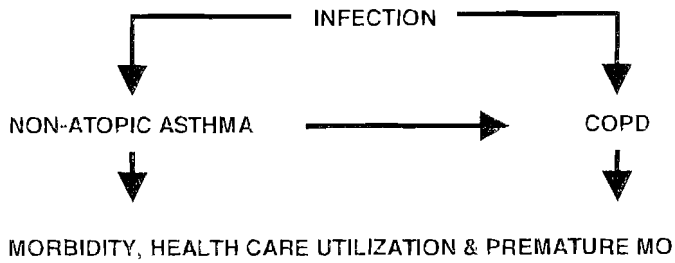

FIGURE 3. An expanded model illustrating the proposed pathways whereby infection influences nonatopic asthma and COPD to produce morbidity, health care utilization, and mortality.

of PMNs.[143] Relevance of these results to clinical asthma is highlighted by additional findings that IL-8 and neutrophil inflammation have been associated specifically with non atopic asthma, whereas eosinophil and mast cell inflammation are present in both atopic and non atopic asthma.[14] It is intriguing to note that a bronchoscopic study of 55 adults with asthma found that mast cells were significantly more prevalent in the 31 subjects who were PCR positive for Mpn and/or Cpn, compared to PCR negative subjects.[116] *In vitro* experiments also demonstrate that Cpn can induce factors relevant to the process of lung remodeling: human bronchial smooth muscle cells infected by Cpn produce IL-6, basic fibroblast growth factor and interferon-beta[144,145] and Cpn-infected human macrophages express matrix metalloproteinase[146] and 92-kD gelatinase.[147] Collectively, these factors may contribute to the development of airway smooth muscle hypertrophy, myofibroblast proliferation and excess extracellular matrix deposition and/or degradation that characterize stages of asthma lung remodeling[148] and airway damage in COPD.

5.3. Summary: *Chlamydia pneumoniae* and Lung Remodeling

Taken together, the studies reviewed in this section lay the groundwork for the hypothesis that persistent Cpn infection in lung tissue can accelerate the process of lung remodeling, the hallmark of COPD. Based on this evidence, an expanded model for the role of infection in the development of obstructive airways disease is presented in Figure 3. Since nonatopic asthma (i.e., the asthma syndrome most likely to be caused by infection) may account for up to 50% of cases, Cpn infection could potentially have a major public health impact on asthma, and ultimately perhaps also on the treatment and/or prevention of other obstructive airways diseases such as chronic bronchitis and emphysema (COPD).

6. CONCLUSION: *Chlamydia pneumoniae*, CHRONIC NONSPECIFIC LUNG DISEASE (CNSLD) AND THE "DUTCH HYPOTHESIS"

According to Vermeire *et al.*,[9] the CIBA Symposium proposed chronic nonspecific lung disease (CNSLD) in 1959 as an umbrella term for chronic

bronchitis, asthma, emphysema and irreversible or persistent obstructive lung disease. In 1961 Orie[23] proposed the "Dutch Hypothesis" which stated that CNSLD represented different expressions of a single disease entity characterized by an hereditary predisposition to develop allergy and bronchial hyper reactivity in response to environmental factors. Prior to the discovery of the Cpn–asthma association, the pros and cons of the "Dutch Hypothesis" were fully debated without the hypothesis being proven or disproven.[9,10] It should be obvious to the reader of this review that the discovery of Cpn as a potential factor in asthma and COPD casts new light on the importance of examining the concept of CNSLD as a pathophysiologic entity.

It is now well established that acute Cpn infection can cause acute bronchitis and pneumonia[149,150] and additional evidence presented herein suggests that lower respiratory tract illnesses caused by acute Cpn infection can develop into asthma and chronic bronchitis.[8,151] Chronic Cpn infection has also been associated with a wide variety of chronic upper-airway illnesses[152,153] as well as with the spectrum of acute and chronic lower-airway conditions including acute bronchitis,[154] asthma and COPD.[81] Taken together, these data suggest a role for Cpn in the entire spectrum of respiratory illnesses embracing the natural history of CNSLD.[19,20,155] Just as early identification and treatment of genital chlamydial infection of women is required to prevent the occurrence of pelvic inflammatory disease and tubal infertility, and timely treatment of eye infection in children is required to prevent blinding trachoma, early identification and treatment of Cpn infection in chronic airways disease will be important to prevent the development of chronic sequelae, if Cpn is confirmed as a treatable cause for even a subset of CNSLD.

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